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Brønsted Acid Catalyzed Asymmetric Aldol Reaction: A Complementary Approach to Enamine Catalysis

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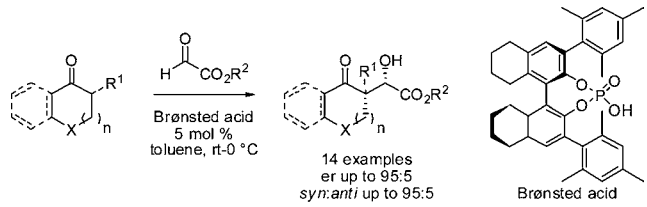
ABSTRACT



A *syn*-enantioselective aldol reaction has been developed using Brønsted acid catalysis based on H_8-BINOL-derived phosphoric acids. This method affords an efficient synthesis of various *β*-hydroxy ketones, some of which could not be synthesized using enamine organocatalysis.

Aldolization is a powerful reaction to create a carbon−carbon bond.[1] The coupling of two simple carbonyl compounds (aldehydes or ketones) leads to a *β*-hydroxy carbonyl subunit. Since this structural moiety is present in numerous natural or synthetically useful products, continuous investigations have been devoted to this reaction for more than a century. While early experiments aimed at broadening the scope of the transformation, research in the last 30 years was focused on stereoselectivity since two new stereogenic centers could be created during the course of the reaction.[2a]

Recently, organocatalysis has emerged as a new tool to control the stereo outcome of aldolization under very mild conditions with a high level of selectivity. The use of strong bases is avoided, as well as metallic Lewis acids, preformed enolates such as silyl enol ethers, or costly chiral auxiliaries. Since the seminal work of Hajos and Parrish,[3] numerous proline derivatives and various polyfunctional amines were successfully evaluated to extend the usefulness of the organocatalyzed cross-aldol reaction.[2b,4] The efficiency of proline-based catalysts relies on the formation of a highly reactive enamine intermediate. Importantly only donors such as moderately hindered aldehydes and unsubstituted ketones gave good yields. In sharp contrast, acetophenone and fused cyclic aromatic ketones (indanone, tetralone...) derivatives are challenging substrates because they would involve twisted less reactive enamines intermediates due to low orbital overlap between the enamine double bond and the nitrogen lone pair (Figure 1). Other challenging substrates are α,*β*-unsaturated ketones, which may trap the amine catalysts through an irreversible 1,4-addition. Interestingly, while no organocatalyst is reported to be effective for the aldol reaction of α,*β*-unsaturated ketones, only two recent contributions

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(1) (a) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095–1120.

(2) (a) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131–173. (b) Zlotin, S. G.; Kucherenko, A. S.; Beletskaya, I. P. *Russ. Chem. Rev.* **2009**, *78*, 737–784.

(3) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496–497.

(4) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

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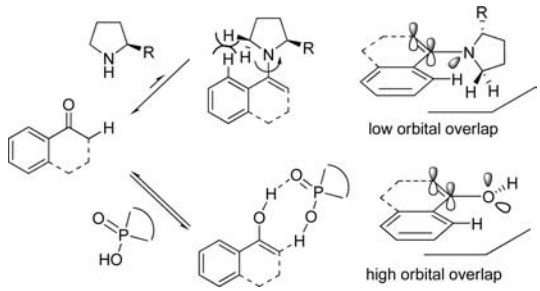


Figure 1. Phosphoric acid catalyisis versus enamine catalysis.

involving chiral zinc or rhodium complexes describe the successful use of methyl vinyl ketone and cyclic enones in asymmetric direct aldol reactions, thus illustrating the challenge represented by those substrates.[5,6]

With this background in mind, we became interested in the alternative well-known acid catalysis. Chiral Lewis acids have been frequently used to control the stereoselectivity of the direct aldol reaction.[7] Witnessing the rapid growth of the use of chiral Brønsted acids, we embarked in an evaluation of those catalysts for the aldol reaction.[8] To the best of our knowledge, among the rare cases of carbonyl group activation[9] such a strategy has been ignored so far.[10]

Initially we screened various Brønsted acids and substrates to identify suitable conditions to further investigate this strategy. Cyclohexanone was selected as a model nucleophile, while ethyl glyoxylate was found to be the most reactive electrophile.[11] Various conditions and catalysts were then tested (Table 1). BINOL-derived phosphoric acid *rac*-**3a** was rapidly identified as a satisfying catalyst candidate when excess ketone was used (Table 1, entry 5).

The reactions carried out under equivalent molar amounts of reagents or excess of glyoxylate afforded the aldol product in slightly lower yields. Surprisingly, concerning the required acidity of the catalyst, stronger acids such as **1** and **2** behaved sluggishly (Table 1, entries 3 and 4).

In order to induce high selectivity in asymmetric transformations when using BINOL-derived phosphoric acids, the chiral BINOL backbone must be substituted by bulky aromatics on the 3,3′ positions. Several 3,3′-disubstituted H_8-BINOL-derived phosphoric acids were thus prepared according to an improved procedure developed in our laboratory.[12]

The introduction of aromatic groups with variable steric hindrance had a strong influence on both diastereo- and enantioselectivity. Phosphoric acid **4a** with a phenyl substituent afforded almost no diastereoselectivity and an average enantioselectivity (er 75:25) for the *syn* diastereoisomer (Table 1, entry 8), whereas hindered acids **3c**[13] (Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$) and **4e** (Ar = 2,4,6-(Me)$_3$C$_6$H$_2$) led, respectively, to improved diastereoselectivity in favor of the *syn* isomer (dr *syn*/*anti* 80:20, Table 1, entries 7) and enantioselectivity (er 86:14) for the major *syn* isomer (Table 1, entry 12).

Next, we screened the reaction conditions to optimize the yield and selectivity of the aldol product. Among the various nonprotic solvents tested (toluene, xylene, THF, Et_2O, Bu_2O, CH_2Cl_2, CH_3CN), toluene was identified to afford the highest diastereo- and enantioselectivity at room temperature (see the Supporting Information). Interestingly, reactions could be performed at 50 °C with little erosion of enantioselectivity (data not shown). Decreasing the reaction temperature had a beneficial impact on the overall selectivity (Table 1, entries 13 and 16). An optimal amount of 5 mol % catalyst was determined, while 1.5 mol % led to slightly decreased selectivity and 10 mol % to no improvement (data not shown). Carrying out the reaction in nearly solventless conditions, using only the toluene provided by the commercial solution of the glyoxylate, led to a significant improvement of both reaction rates and selectivities (dr *syn*/*anti* 70:30 and 93:7 er for the *syn* isomer, Table 1, entry 14).

Recycled catalyst, easily recovered by column chromatography in 80% yield, performed with the same level of selectivity (Table 1, entry 15). The absolute configuration of the main isomer was acertained by comparison with literature data.[14]

Interestingly, the observed diastereoselectivites were moderated in favor of the *syn* diastereoisomer, so we decided to

(5) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602–8603.

(6) Mizuno, M.; Inoue, H.; Naito, T.; Zhou, L.; Nishiyama, H. *Chem.—Eur. J.* **2009**, *15*, 8985–8988.

(7) (a) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497–2500. (b) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178.

(8) (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (b) Terada, M. *Chem. Commun.* **2008**, *35*, 4097–4112. (c) Terada, M. *Synthesis* **2010**, 1929–1982.

(9) (a) Xu, S.; Wang, Z.; Wang, X.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2840–2843. (b) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593–596. (c) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084–12085. (d) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097–2100. (e) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626–9627. (f) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798–6801. (g) Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4226–4228. (h) Lu, M.; Zhu, D.; Lu, Y.; Zeng, X.; Tan, B.; Xu, Z.; Zhong, G. *J. Am. Chem. Soc.* **2009**, *131*, 4562–4563. (i) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056–4057. (j) Sun, F.-L.; Zeng, M.; Gu, Q.; You, S.-L. *Chem.—Eur. J.* **2009**, *15*, 8709–8712.

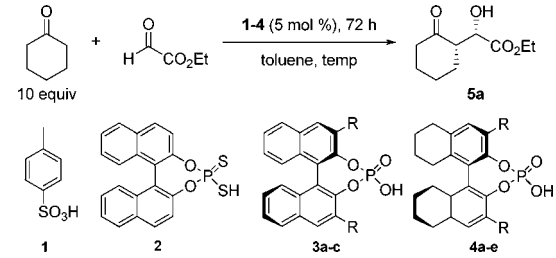
(10) For previous asymetric Mukaiyama aldol reactions catalyzed with chiral Brønsted acids, see: (a) Cheon, C. H.; Yamamoto, H. *Org. Lett.* **2010**, *12*, 2476–2479. (b) García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363–4366. (c) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6130–6133. (d) Gondi, V. B.; Hagihara, K.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 776–779. (e) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org Biomol. Chem.* **2005**, *3*, 3284–3289. For previous activation of ethyl glyoxylate by chiral phosphoric acids, see: (f) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122–4125. (g) Momiyama, N.; Tabuse, H.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 12889–12890.

(11) Other electrophiles were tested (2-methylpropanal, 1-butanal, chloral, 2- and 3-pyridine carboxaldehyde, benzaldehyde, phenyl glyoxal), and only traces of product were detected. Ethyl trifluoropyruvate delivered 42% yield.

(12) Pousse, G.; Devineau, A.; Dalla, V.; Humphreys, L.; Lasne, M.-C.; Rouden, J.; Blanchet, J. *Tetrahedron* **2009**, *65*, 10617–10622.

(13) During the revision process of the manuscript, the octahydrogenated analogue **4f** (R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$) was prepared and the obtained selectivities were identical to those of **3c** (at 0 °C: 75% yield, 80:20 dr, 89:11 er).

Table 1. Optimization of the Aldol Reaction Conditions



entry[a]	catalyst	R	temp (°C)	yield[b] (%)	*syn*/*anti*[c]	er/*syn*[d] (%)
1	none		20	0		
2	CF_3CO_2H		20	58	35:65	
3	**1**		20	18	50:50	
4	*rac*-**2**[e]		20	40	50:50	
5	*rac*-**3a**[e]	H	20	75	50:50	
6	**3b**	1-naphthyl	20	70	55:45	72:28
7	**3c**	2,4,6-(*i*-Pr)$_3$C$_6$H$_2$	20	78	80:20	85:15
8	**4a**	Ph	20	60	55:45	75:25
9	**4b**	1-naphthyl	20	65	60:40	73:27
10	**4c**	9-phenanthryl	20	78	55:45	76:24
11	**4d**	2-*i*-PrC$_6$H$_4$	20	77	66:33	81:19
12	**4e**	2,4,6-(Me)$_3$C$_6$H$_2$	20	72	55:45	86:14
13	**4e**	2,4,6-(Me)$_3$C$_6$H$_2$	0	58	60:40	91:9
14	**4e**	2,4,6-(Me)$_3$C$_6$H$_2$	0[f]	55	70:30	93:7
15	**4e**	2,4,6-(Me)$_3$C$_6$H$_2$	0[f,g]	50	70:30	95:5
16	**3c**	2,4,6-(*i*-Pr)$_3$C$_6$H$_2$	0[f]	50	80:20	89:11

[a] A concentration of 0.4 M was used. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by chiral HPLC. [e] Racemic catalyst was used. [f] A concentration of 10 M was used. [g] Catalyst **4e** was recycled from previous experiments.

explore the generality of this new Brønsted acid catalyzed aldolization.

First, the reaction scope was probed by changing the nature of the glyoxylate partner. Isopropyl and benzylic glyoxylates led to slightly lower selectivities and reactivity (Table 2, entries 1 and 2). Pyrrolidine glyoxamide failed to react under selected reaction conditions.

Finally, we investigated several nucleophile partners of the reaction. Simple ketones such as pentan-2-one, tetrahydrothiopyran-4-one, tetrahydropyran-4-one, and cyclopentanone gave slightly lower selectivities than cyclohexanone under optimized reaction conditions (Table 2, entry 3−6). Since those substrates including cyclohexanone are routinely used in aldol reactions, we were most interested in testing compounds that are known to be challenging, particularly when enamine catalysis is involved.

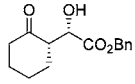
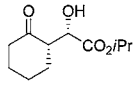
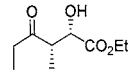
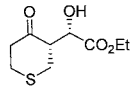
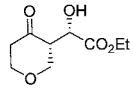
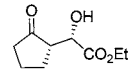
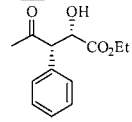
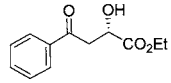
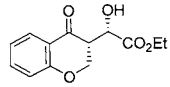
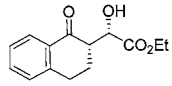
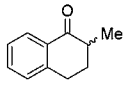
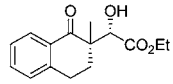
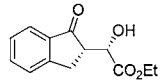
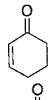
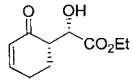
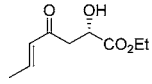
Phenylacetone afforded the expected branched aldol product with complete regiospecificity with 83:17 er for the *syn* isomer at 10 °C (Table 2, entry 7). More interestingly, acetophenone, 4-chromanone, tetralone, and crowded 2-methyltetralone were found to be suitable substrates, giving average to good yields of aldol products with up to 85:15 er for the major *syn* isomer (Table 2, entries 8−11). Importantly, those substrates have never been reported in any organocatalyzed aldol reactions, probably due to the difficult formation and poor reactivity of the enamine intermediate if one would use a proline derivative as catalyst. Although lower reactivity was found with these compounds, a quaternary center was formed by the condensation of 2-methyltetralone with ethyl glyoxylate, such a reaction being usually carried out under Mukaiyama's conditions. With indanone only the *syn* isomer was isolated with 88:12 er at 10 °C (Table 2, entry 12).

Encouraged by the previous results, we next tested α,β-unsaturated ketones using Brønsted acid catalysis. We found that cyclohexenone and 3-penten-2-one delivered the expected aldol products in 78−70% yield and up to 88:12 er (Table 2, entry 13 and 14). No compound corresponding to a possible vinyloguous reaction was observed. Notably, no elimination byproduct was detected in spite of the known instability of such aldol products. These two examples represent rare cases of an asymmetric direct aldol reactions with enones, without recourse to their silyl enol ethers derivatives.

In summary, we have uncovered the first asymmetric Brønsted acid catalyzed direct aldol reactions. Moderate to excellent diastereo- and enantioselectivity have been achieved using chiral H_8-BINOL-derived phosphoric acids (up to 95:5 dr and 95:5 er) which may render this approach synthetically attractive for the synthesis of a more complex molecule. The sense of the relative stereoselection is the opposite as the one in similar proline-catalyzed reactions, favoring the *syn*

(14) See the Supporting Information for more details.

Table 2. Scope of the Aldol Reaction. Variation of the Electrophile and the Nucleophile

entry[a]	ketone	major product		conditions[a]	yield[b]	*syn*:*anti*[c]	er:*syn*[d]
1			**5b**	10 M, 0 °C[e]	42	70/30	92:8
2			**5c**	10 M, 0 °C[f]	51	65/35	89:11
3			**6**	10 M, 20 °C	50	85/15	83:17
4			**7**	5 M, 10 °C	44	50/50	85:15
5			**8**	10 M, 10 °C	54	75/25	85:15
6			**9**	0.4 M, 50 °C	86	70/30	80:20
7			**10**	10 M, 10 °C	83	90/10	83:17
8			**11**	10 M, 20 °C	52	-	81:19
9			**12**	5 M, 10 °C	60	70/30	74:26
10			**13**	10 M, 10 °C	50	85/15	85:15
11			**14**	0.4 M, 50 °C	78	55/45	78:22
12			**15**	5 M, 10 °C	79	95/5	88:12
13			**16**	10 M, 20 °C	70	70/30	88:12
14			**17**	0.4 M, 50 °C	70	-	79:21

[a] Reaction conditions: ethyl glyoxylate, ketone (10 equiv), **4e** (5 mol %), toluene, 72 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] Benzyl glyoxylate was used. [f] Isopropyl glyoxylate was used.

isomer.[15] These results clearly demonstrate the complementary character of Brønsted acid catalysis toward enamine (proline) catalysis. In particular, many unreactive substrates in enamine-type organocatalysis afford the aldol product under those conditions. Noteworthy are the examples of 2-methyltetralone and enones. Finally, the catalyst can be easily recycled with equivalent performances. Studies of the mechanism and synthetic applications of this reaction are currently under investigation.

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Supporting Information Available: Experimental procedure, characterization data, HPLC charts, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Only in rare cases were organocatalysts reported to be general *syn*-selective aldol catalysts. (a) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074–3075. (b) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7606–7608. α-Hydroxy ketones are known to deliver *syn* selectivity; see: (c) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288–289. (d) Palyam, N.; Majewski, M. *J. Org. Chem.* **2009**, *74*, 4390–4392.